(3)
Environmental Technology, Vol. 12, pp 193-208
© Publications Division Selper Ltd., 1991

WEAKNESSES IN RECENT RISK ASSESSMENTS OF ENVIRONMENTAL TOBACCO SMOKE

P.N. LEE

P.N.Lee Statistics & Computing Ltd., 17 Cedar Road,Sutton, Surrey SM2 5DA, U.K.

(Received 25 June 1990, Accepted 11 January 1991)

ABSTRACT

Epidemiological evidence of increased lung cancer risk in never smokers married to smokers has been used to estimate annual deaths from environmental tobacco smoke (ETS) exposure. Such estimates are very much higher than those based on dosimetric considerations and misleadingly ignore major weaknesses in the epidemiology. Some authors overestimate total lung cancers occurring in never smokers. There is no scientific basis for extending risk assessments to include deaths from other causes, from workplace exposure to ETS, and among ex-smokers. Recent risk assessments by Wells, by Repace and Lowrey, and by Kawachi and colleagues are given particular attention.

INTRODUCTION

In 1986 four authorities reviewed the evidence on the relationship of environmental tobacco smoke (ETS) and health (1-4). There was agreement that there was inadequate evidence to determine whether ETS caused heart disease or cancers other than the lung. With regard to lung cancer views were more conflicting. The International Agency for Research on Cancer (1), while noting that "several epidemiological studies have reported an increased risk of lung cancer in non-smoking spouses of smokers" pointed to "substantial difficulties" and errors that "could arguably have artefactually depressed or raised estimated risks" so that each study "is compatible either with an increase or with an absence of risk". The Australian National Health and Medical Research Council (2) noted that "the evidence that passive smoking causes lung cancer is strongly suggestive" and, although pointing to difficulties in many studies that "preclude a conclusive interpretation", stated that "passive smoking gives rise to some risk of cancer". The US Surgeon General (3) concluded that "involuntary smoking is a cause of lung cancer" but that quantification of the risk for the US population "is dependent on a number of factors for which only a limited amount of data are currently available". The US National Research Council (4) noted that a "summary estimate from epidemiological studies places the increased risk of lung cancer in non-smokers married to smokers compared with non-smokers married to non-smokers at about 34%" and considered that, though "to some extent, misclassification bias may have contributed to the results reported in the epidemiological literature", the "bias is not likely to account for all of the increased risk".

Although one of the four authorities felt it premature to conclude cause and effect, and two who thought cause and effect could be concluded, felt it could not be quantified, there has been an increasing tendency to carry out risk assessments to estimate annual numbers of deaths due to ETS. The purpose of this paper is to underline a number of problems in conducting such risk assessments, and to comment critically on three that have recently been published. The first, by Wells (5), estimated that annually in the United States 46,000 deaths per year occurred among non-smokers (i.e. never plus ex-smokers combined) due to ETS exposure at home and at work. 3,000 were from lung cancer, 11,000 from other cancer and 32,000 from heart disease. The second, by Kawachi and colleagues (6), estimated that annually in New Zealand 273 deaths per year occurred among never smokers, 30 from lung cancer and 243 from ischaemic heart disease; 95 deaths were from at home exposure and 178 from at work exposure. The third risk assessment, by Repace and Lowrey (7), was based on a review of nine

other risk assessments for lung cancer. They noted that "excluding one study whose estimate differs from the mean of the others by two orders of magnitude, the remaining risk assessments are in remarkable agreement. The mean estimate is approximately 5000 ± 2400 non-smokers' lung cancer deaths per year in the US".

This paper starts by discussing risk assessment for lung cancer among never smokers based on epidemiological data in relation to spouse smoking, this being the area most intensively studied. Following this problems resulting from extending the risk assessment to cover other diseases are discussed, as are those caused by considering workplace as well as at home ETS exposure. Finally, some other issues are considered.

LUNG CANCER IN NEVER SMOKERS IN RELATION TO ETS EXPOSURE FROM THE SPOUSE

An up-to-date review of the evidence (8) shows there are 27 epidemiological studies of lung cancer (involving nine or more cases) in which risk in never smokers could be related to the smoking status of the spouse (or in five studies to an alternative index of at-home exposure). Eleven studies were conducted in the US, eleven in Asia and five in Europe, involving a total of 2350 lung cancer cases with relevant data, 90% of these being females. 26 of the 27 studies provide estimates of relative risk in relation to this index of ETS exposure for females; values range from just under 1.0 to just over 2.0. Five are statistically significantly positive and 20 estimates are greater than 1.0. Taken as a whole the data show a positive relationship - the median is about 1.25. Based on 17 of these studies, using formal meta-analytic techniques which weighted studies on sample size but not on quality of evidence, Wells (5) gave an average relative risk of 1.44, with 95% confidence limits 1.26 to 1.66. The data for males are more variable, being based on 11 studies often with small numbers of deaths. Seven relative risks were greater than 1, one significantly so, with one equal to 1 and three less than 1. The median is similar to that for females.

The epidemiological evidence has been used for the risk assessments of Wells (5) and Kawachi *et al* (6). It has also been used for a number of the risk assessments cited by Repace and Lowrey (7). This is only valid if the epidemiological evidence itself is sound and not subject to material bias. In order to investigate this issue, two questions will be addressed; first, "Is the magnitude of the risk plausible based on what is known about the extent of exposure?" and second, "Are there weaknesses and sources of bias in the epidemiology which could invalidate the approach?"

Dosimetric considerations.

If lung cancer risk, relative to a non ETS exposed never smoker, is RE in an ETS exposed never smoker and RS in an ever smoker, then the ratio of excess risks X=(RE-1)/(RS-1) is an indicator of the relative effects of ETS exposure alone and of smoking. Since risk associated with smoking is approximately proportional to number of cigarettes smoked, one might expect, were the epidemiology unbiassed, that X would be similar to the ratio of relevant smoke constituents from ETS exposure and from smoking. Table 1 shows, in rank order, estimates of X based on data for 18 studies in females and 7 studies in males. In females, almost half (8/18) of estimates are 0.2 or greater with the median value 0.14. For males, the results vary more and are based on many less data points, but the conclusions to be drawn are similar - namely that the epidemiological evidence, if unbiassed, suggests that the extent of exposure from ETS (from spousal smoking) is something like 10-20% of that from active smoking.

It is clear the ratio of exposure from ETS and exposure from active smoking is much lower than 10-20% for those smoke constituents that are commonly used as markers. In a large nationally representative study in the UK (27), mean salivary cotinine levels in non-smokers married to non-smokers, in non-smokers married to smokers and in smokers were respectively 1.22, 3.78 and 331 ng/ml in males and 0.76, 2.21 and 328 ng/ml in females, giving a relative exposure for ETS to active smoking of 0.8% in males and 0.4% in females. Repace and Lowrey (7) give a slightly higher figure, noting that non-smokers have of "the order of 1% of nicotine uptake of smokers" but it is still an order of magnitude less than the 10-20% one requires to align with the epidemiology. Differences in clearance rates of cotinine reported between non-smokers and smokers are too small to affect this gross discrepancy materially; in any case, since the half-life seems to be longer in non-smokers it would increase the discrepancy (28), not reduce it as Repace and Lowrey (7) claim.

TABLE 1 Comparability of relative risks due to ETS exposure (from spouse) and active smoking

Study	(ref)	Sex	RE*	RS**	X+
Inoue	(9)	Female	2.55	4.25	0.48
Geng	(10)		2.16	4.18	0.36
Trichopoulos	(11)		2.08	4.37	0.32
Akiba	(12)		1.52	3.24	0.23
Brownson	(13)		1.82	4.75	0.22
Koo	(14)		1.55	3.56	0.21
Lam 1	(15)		2.01	5.94	0.20
Hole	(16)		1.89	5.43	0.20
Lam 2	(17)		1.65	4.97	0.16
Hirayama	(18)		1.38	4.12	0.12
Gao	(19)		1.19	3.15	0.09
Wu	(20)		1.20	3.31	0.09
Correa	(21)		2.07	14.10	0.08
Humble	(22)		2.34	28.53	0.05
Svensson	(23)		1.26	7.17	0.04
Lee	(24)		1.03	4.70	0.01
Buffler	(25)		0.80	5.91	-0.04
Chan	(26)		0.75	3.07	-0.12
Akiba	(12)	Male	2.10	3.21	0.50
Hirayama	(18)		2.34	4.39	0.40
Hole	(16)		3.52	15.88	0.17
Humble	(22)		4.19	29.36	0.11
Correa	(21)		1.97	30.15	0.03
Lee	(24)		1.31	12.02	0.03
Buffler	(25)		0.51	7.03	-0.08

* Risk of ETS exposed never smoker relative to non ETS exposed never smoker

** Risk of ever smoker relative to non ETS exposed never smoker

\+ Ratio of excess risks, e.g.for first study 0.48 = (2.55-1)/(4.25-1)

N.B. Risks given are unstandardised for age since standardised estimates were not available in many studies and generally differed little from unstandardised estimates where both were available.

Estimates of relative exposure based on inhaled smoking-related particulates show an even greater discrepancy. Arundel *et al* (29) have estimated that for the US average daily inhaled particulate ETS exposure for all never smokers is 0.62 mg/day for men and 0.28 mg/day for women as against 387 mg for men and 311 mg for women who currently smoke. Since ETS exposure of exposed non-smokers is about 3 times that of all non-smokers (27), one can calculate that the ratio of average exposure for ETS to active smoking is about 0.4% in men and 0.2% in women, similar to an estimate of 0.3% given by Repace and Lowrey (7) based on their own work.

Arundel *et al* (29) pointed out retention of smoking related particulates is much higher in smokers (80%) than in non-smokers(11%). They estimated a relative exposure for ETS to active smoking of around 0.03-0.04% (29). Using radiotracer techniques, a similar, very low ratio of 0.02% has been estimated based on particulate deposition in the trachea-bronchial region (30).

While both ETS and mainstream smoke contain a wide variety of chemicals, and relative exposure of passive and active smokers will vary quite widely according to which chemical is used as the marker - the factor being higher for vapour phase than for particulate phase compounds (31) - there is certainly strong evidence of a marked discrepancy between the epidemiology and dosimetry. Indeed, since it is commonly believed lung cancer in smokers is associated with deposition of particulate matter in the lung - the basis of "tar" reduction programmes - the discrepancy seems very large, by two or even three orders of magnitude.

One implication is that risk assessments based on dosimetric evidence are likely to give substantially lower estimates than those based on the epidemiological evidence. Another implication is that it gives reason to doubt the epidemiology, and to look for sources of bias.

Risk assessments based on dosimetry versus those based on epidemiology.

Let us consider the situation with regard to the three risk assessment papers which are being studied in detail. All three have different approaches.

Kawachi *et al* takes the epidemiology at face value and do not attempt risk assessment based on dosimetric evidence (except vide infra to adjust relative risks for at home exposure to those for at work exposure). The discrepancy between the dosimetry and the epidemiology is not even mentioned.

Wells (5) also bases his risk assessment on the epidemiology. However he does note that the mortality observed for passive smoking is "rather high" relative to the deposited dose of particulate, contrasting relative factors for passive to active smokers of 0.25% for "smoke retention" (Arundel's figures cited above suggest 0.03-0.04%) and 2.9% for lung cancer (Table 1 suggests 10-20%). He believes the differences are due to differences in chemistry and physics between active and passive smoking, and essentially does not doubt the validity of the epidemiology.

Repace and Lowrey (7) review risk assessments based both on dosimetric and epidemiological evidence. While this should have revealed major differences between estimates based on the two methods of risk assessment they in fact claim "remarkable agreement". There are many reasons for this erroneous conclusion:

i) They rejected the estimate of Arundel *et al* (29), based on retained particulate matter, because it differs from the mean of the others by two orders of magnitude.

ii) They misquote Robins' work in the NRC report (4). They cite his estimates of 2500-5200 US deaths in lifelong non-smokers per year from passive smoking as being dosimetrically based when in fact they clearly are epidemiologically based. Robins also provides much lower estimates of 45-396 deaths based on respirable suspended particulates, but Repace and Lowrey totally ignore these.

iii) They quote an early paper by Fong (32), which assumed that the extent of exposure from ETS was of order 2% to 8% that from active smoking, a relative factor far higher than indicated by the more recent data summarized in the previous section.

iv) They omit their own dosimetrically based estimate because it is "inconsistent with the epidemiology of passive smoking". It is hardly surprising they get "remarkable agreement" if they reject estimates that do not agree!

Table 2 presents the various estimates for the studies reviewed by Repace and Lowrey (7). The epidemiologically based estimates are reasonably consistent and high. The dosimetrically based estimates are much lower. How much lower depends on the smoke constituent used for extrapolation.

Weaknesses of the epidemiology.

Epidemiology is imprecise. Various sources of bias can produce spurious relative risks of 2 or even more (38). Since the relative risks seen for ETS exposure are well within this range, and since they seem inconsistent with the dosimetric evidence, it is important to examine the epidemiological evidence critically. Six potential sources of bias are considered below.

Misclassification of diagnosis.

Of the 27 epidemiological studies of ETS and lung cancer, three were prospective and based diagnosis on death certificates, and only 15 used only (or virtually only) histologically confirmed cases. Faccini (39) has discussed the dangers of misdiagnosis, particularly of primary breast cancer as lung adenocarcinoma. The magnitude and extent of bias from this source is, however, unclear. Random misdiagnosis would tend to reduce the relative risk, but differential misdiagnosis might increase it. In theory differential misdiagnosis might occur if a risk factor for the misdiagnosed disease is correlated with ETS exposure, or if knowledge of ETS exposure by the doctor affects diagnostic procedures, but there is no direct evidence of this.

Misclassification of ETS exposure.

None of the studies had any objective measure of ETS exposure, either from ambient air measurements in the home or workplace or from measurements of levels of smoke constituents in body fluids. All information came from questionnaires. While random misclassification of exposure will tend to dilute associations, it is possible that in case-control studies some recall bias might have occurred, with cases overestimating exposure relatively to

controls in an attempt to rationalize their disease. This would probably have been less important for relatively "hard" questions such as those relating to whether the spouse smoked than for more "soft" questions on extent of exposure.

Publication bias.

There is strong reason to believe (40) that scientists are less likely to submit, and journals less likely to accept, papers showing no association than those showing a positive association. If so, published evidence tends to overestimate the true association of a factor with a disease. Since ETS has been the subject of much attention in recent years and since a relatively large number of unpublished null studies would be needed to counterbalance the high proportion of studies of spouse smoking and lung cancer showing a positive association, it would seem unlikely non-reporting bias could fully explain the overall positive relative risk. However the fact that the studies showing the highest relative risk are based on significantly smaller numbers of cases than the studies showing the lowest relative risks (8) is consistent with the notion that small null studies do not get published, and suggests some publication bias exists.

TABLE 2 Estimated number of lung cancer deaths occurring in US never smokers from ETS exposure in 1988 (adapted from Repace and Lowrey (7))

Study	(ref)	Method of estimation	Estimate *
Wald	(33)	Epidemiological	5210
Repace & Lowrey	(34)	Phenomenological **	4310
Robins	(4)	Epidemiological	4150
Wigle	(35)	Epidemiological	3650
Kuller	(36)	Epidemiological	3500
Wells	(5)	Epidemiological	2130
Fong	(32)	Dosimetric - 2% to 8% of effect	1860
Russell	(37)	Dosimetric - nicotine	710
Repace & Lowrey	(34)	Dosimetric-respirablesuspended particulates	490
Robins	(4)	Dosimetric +	240
Arundel	(29)	Dosimetric - retained particulate matter	40

* As given in (7), rounded, or converted from estimate for nonsmokers. Dosimetric estimate for Robins study added.

** Based on comparison of lung cancer rates in never smoking SDAs (Seventh Day Adventists) and non SDAs (uncorrected for numerous lifestyle factors on which SDAs and non SDAs are known to differ).

\+ Assuming a non-exposed non-smoker inhales the equivalent of 0.01 cigarettes per day. Robins gives 0.0001-0.005 cigarettes per day for the equivalent in terms of respirable suspended particulates.

Poor design of some studies.

Of the 27 studies which provided information on ETS and lung cancer, 24 were of case-control design. There were clear weaknesses in design in a number of the case-control studies. One study (10) did not even state what the control group was. Four studies (9, 12, 21, 25) included some patients or decedents with smoking associated diseases in their control group. More seriously there were systematic differences in study procedure between cases and controls in a number of studies. In three studies where the case might have been alive or dead (13, 22, 41) the controls were not matched on vital status. Two studies (11, 15) used cases and controls from different hospitals. Two studies (17, 23) interviewed cases in hospital and some or all controls elsewhere. In three studies (13, 21, 22) the proportion of next-of-kin respondents was substantially higher for cases than controls. Although difficult to quantify the effect of such procedural differences it is notable that for females the observed relative risk in the eight studies showing differences was higher (median 1.9) than in the 17 studies where like was being compared with like (median 1.2, p on rank test <0.05). It is also worth noting that three studies (12, 25, 42) obtained a high proportion of responses from next-of-kin and that in one of these (42), no association between lung cancer risk and spouse smoking was seen when the

subject herself reported the information, but a 3-fold relative risk was seen when the information was obtained from a daughter or a son.

Confounding.

There were 22 studies in which the index of ETS exposure used was smoking by the husband. One would have thought that the standard procedure would have been to present an age-adjusted comparison of married never smoking women whose husbands were non-smokers with married never smoking women whose husbands were smokers, and to also present a relative risk adjusted further for other potentially confounding factors known to affect risk of lung cancer. It was clear this standard procedure was not kept to. About half of these studies included unmarried women in their non-exposed group so that there was a confounding between marital status and ETS exposure. Three of the 22 studies (11, 15, 43) and also one of the other five (26) did not adjust for age at all while in three others (10, 17, 21), although cases and controls were age-matched initially, the error was made of failing to age adjust after the never smokers were selected out. Almost half the studies failed to take into account any other confounding factors and of the remainder most looked at only quite a limited number of possible such factors. Those few studies which looked at a reasonable number of confounders were generally those where no significant effect of ETS exposure had been seen anyway. Koo (44) compared never smoking women whose husbands did or did not smoke on a wide range of factors and found that those whose husbands did not smoke were "better off in terms of socio-economic status, more conscientious housewives, ate better diets, and had better indices of family cohesiveness".

Misclassification.

It is amply documented that active smoking is positively associated with lung cancer and also that smokers tend preferentially to marry smokers more often than would be expected by chance. As a result, even if ETS had no effect whatsoever on lung cancer risk, a spurious positive association between spouse smoking and lung cancer risk will be seen if a proportion of ever smokers are misclassified as never smokers (27). The relationship between the magnitude of this bias and the misclassification rate can be calculated theoretically given the degree of between spouse smoking concordance, the observed proportion of ever smokers, the observed proportion of never smokers who are married to smokers, and the observed relative risk in relation to active smoking. Table 3 shows this relationship for four scenarios: US women, US men, Asian women and Asian men. The misclassification bias is much larger where the proportion of smokers is larger, and where the relative risk in relation to active smoking is larger. In order to achieve a bias of 1.4 for example, one would need less than a 1% misclassification for US men, about a 2% misclassification for Asian men, about a 5% misclassification for US women and about a 30% misclassification for Asian women. Elsewhere (44) I have reviewed in detail the published evidence on the levels of misclassification actually determined in over 100 studies. In studies of self-reported non-smokers under no special pressure to deny smoking, biochemical tests suggested that on average around 4% were actually current smokers, with 1 to 2% current regular smokers. In addition to the misclassified current smokers, studies in which subjects were asked questions on multiple occasions have shown a somewhat larger number of ex-smokers misclassified as never smokers. The evidence is certainly consistent with misclassification bias being of major importance in the US (and European) studies. However there is virtually no good evidence on misclassification rates in Asian populations. There has long been speculation that rates may be particularly high among women in Japan, where smoking is not considered socially acceptable. A survey of Tokyo University freshwomen (46), among whom 55% of smokers reported that their family did not know they smoked, tends to confirm this. However until cotinine studies are conducted to find out the true situation the extent of bias caused by misclassification in Asian studies will remain unclear.

Misclassification also leads to overestimation of the total number of lung cancers among never smokers. This is considered below under "other issues".

Conclusion.

The answers to the two questions posed earlier are clear. The epidemiology has indicated a magnitude of risk in relation to spouse smoking that is implausibly large compared with what is known about the extent of ETS exposure involved. There are clear weaknesses and sources of bias in the epidemiology which could invalidate risk assessments based on it. The most important of these are misclassification bias and failure properly to compare like with

like in case-control studies, but failure to properly take confounding variables into account and publication bias are also relevant.

All three risk assessments criticised in this document take the epidemiology virtually at face value, with no real discussion at all of its weaknesses. Thus Kawachi *et al* (6) mentions only publication bias (and dismisses it), while Wells (5) considers only misclassification bias (and then inadequately corrects for it). Repace and Lowrey (7) do not discuss any sources of bia at all (though some of the authors whose studie they review do so). No reasonable scientifi criteria are used to decide what constitutes a vali study before it can be included in a ris assessment - studies conducted with complet disregard of basic scientific principles ar included as if they were as valid as carefull designed studies.

TABLE 3 Bias due to misclassification in four scenarios.

Scenario	% Ever Smoked	% ETS Exposed	RR for Smoking	Misclassification Rate	Bias
US women	49.0	54.3	6.73	1%	1.06
				2%	1.12
				5%	1.35
				10%	2.02
US men	77.1	38.7	11.83	1%	1.52
				2%	2.38
Asian women	24.5	56.9	2.99	10%	1.07
				25%	1.26
				40%	1.73
				50%	2.82
Asian men	80.8	6.6	3.48	1%	1.20
				2%	1.42
				5%	2.36

N.B. No effect of ETS and between spouse concordance ratio of 3.0 assumed. % ever smoked, % ETS exposed and RR (relative risk) for active smoking estimated from those studies providing relevant data. See (8) for further details.

EXTENDING RISK ASSESSMENT TO COVER DISEASES OTHER THAN LUNG CANCER

Heart disease.

In the risk assessment by Wells (5), heart disease deaths formed 70% of the total. In that by Kawachi *et al* (6), they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion.

Wells (5) cites data from six published studies (18, 24, 47-50) and one unpublished study (51). Of these seven studies, five (16, 24, 48, 50, 51) were based on very much smaller number of deaths/cases than the other two (18, 49) so that they contribute very little to the overall meta-analysis. While some further small studies have been published since (see 8), none are large. For this reason it is worth taking a detailed look at the two larger studies.

The largest of these studies was by Helsing *et al* (49). This involved more heart disease deaths among non-smokers than all the other studies combined. It reported a 24% increase in heart disease risk in women exposed to ETS, based on 988 deaths, and a 31% increase in men, based on 370 deaths. Many features of the study and the results render any conclusion that ETS causes heart disease most insecure:

i) The comparison was of people who lived with a smoker and of those who did not, with no direct adjustment for the number of people in the household. Clearly the larger the household, the more likely it is to contain a

smoker, so any risk factors related to household size could contribute to the association.

ii) The study was not a properly conducted prospective study, in that data were only collected on whether a given subject had or had not died in Washington County over the 12-year period. Differences in smoking habits and disease status between those who left the county and those who did not may have caused substantial bias.

iii) There was no dose-response relationship in the exposed groups. Indeed, in men the risks (relative to the non-exposed) were somewhat lower with increasing exposure score.

iv) Adjustment for effects of age, marital status, years of school and quality of housing used a procedure that was unclear and which had a huge effect. Thus in women, the passive smoke exposed group had a crude heart disease death rate 34% lower than the non-exposed group. After adjustment it was 24% higher. Such a large effect of adjustment makes one wonder just how contingent the reported results were on the exact list of confounding variables included, the statistical technique used for adjustment, and the accuracy with which the confounding variables were measured.

v) A whole range of factors have been related to heart disease. Among major factors not considered in the study were hypertension and cholesterol level.

While it is difficult to determine the relative importance of the features listed above, it is clear that one must have very considerable reservations about the results from this study.

The Japanese prospective study of Hirayama (18) is superficially very good, being very large, having a long follow-up period and being apparently reasonably representative. However, following detailed scrutiny given to his study following the 1981 paper (52) which really brought ETS to public attention, a number of authors have identified various weaknesses (53, 54, 55). His questionnaire was extremely short and crude by modern standards, severely limiting the number of risk factors studied and the depth to which they could be investigated. The population was only interviewed once with no changes in habits recorded in 16 years. The mortality of his allegedly representative population is too low to reconcile satisfactorily with national rates, indicating that tracing of deaths was incomplete, with deficits varying by age and marital status (53). His statistical presentation is inadequate in a number of ways: the methods used were not appropriate for analysis of long-term cohort studies; rates for heart disease in women were age adjusted to their husband's age rather than their own age; and some basic mistakes in analysis were made. One error, noted in 1981 (54), resulted in enormous inflation of the significance of the lung cancer association. A second, noted more recently (55), concerned the total inconsistency of results for heart disease reported in 1981 and 1984, and was only resolved by Hirayama (56) admitting his earlier data were in error. A number of approaches have been made to Hirayama to release his data for independent verification of his findings by more appropriate statistical methods, but Hirayama has always refused to release his data, which only casts more doubt on his findings. While his findings show a 16% increased risk of heart disease in never smoking women married to smokers which is marginally significant when a dose-related trend test is used, it is difficult to place much faith in his findings.

Although it has been demonstrated above that the risk assessment for heart disease essentially rests on the results from two studies, both of which seem unreliable, a number of other general points can be made. First, there are a very large number of risk factors for heart disease. It is evident that adjustment for these factors in the studies has always been incomplete, and often seriously incomplete. Second, the extent of the association seen in some of these studies, which in some cases is close to that reported in relation to active smoking, is implausibly high when viewed against the extent of the association seen in relation to active smoking. Third, there is a major danger of publication bias. It is notable that the literature is still relatively sparse despite the numerous ongoing studies of heart disease and the fact that heart disease in a non-smoker is probably 50 times or so more common than lung cancer in a non-smoker. Any prospective study that has reported on lung cancer clearly could have done so for heart disease. The fact that the American Cancer Society million person study, which reported for lung cancer (57), has not reported any results on the relationship of heart disease to ETS can reasonably be read as implying no relationship was found in that study. If this is in fact true, and its results were published, the picture from the meta-analysis would change dramatically since the study would involve so many deaths from heart disease in non-smokers.

Cancer other than the lung.

Kawachi *et al* (6) did not include deaths from cancers other than the lung in their risk assessments, but Wells (5) did, although he only made estimates for females since he considered data for males to be too sparse. In fact, there is by now rather more evidence available than Wells considered, and the picture is completely unconvincing as to the effect of ETS exposure.

Of 10 studies providing some evidence, six give no real indication of an effect of ETS. These included two moderate sized case-control studies of bladder cancer (58, 59) which both gave relative risks close to unity, a case-control study of cervix cancer (60) which found no association with spouse smoking after controlling for smoking by the female subject, and a prospective study (47) which found a non-significant relative risk of 1.20 for cancers other than the lung based on 43 deaths. Another study showing no effect was the case-control study of Miller (61) from which an age-adjusted relative risk of 0.97 for lung cancer in relation to husband's smoking history could be calculated. It is interesting to note that Miller, while presenting data by age, did not age-standardise, and gave a relative risk of 1.40, while Wells (5), though he did age-standardise, unaccountably used data for unemployed rather than all women, giving a non-significant, relative risk of 1.25. The largest study showing no effect was the Washington County study on which the Helsing heart disease results (49) were based. A later paper (62) reported that relative risks for all cancer for living with a smoker were 1.01 in males, based on 115 deaths, and 1.00 in females, based on 501 deaths.

Turning now to the four studies that provided at least some suggestion of an effect, the smallest was that by Reynolds *et al* (63). This prospective study found no association between smoking by the spouse and risk of cancer in men, not giving detailed results. In women, a positive association was found, but this was only of marginal significance (p=0.035), and the relative risk of 1.68 had quite wide confidence limits, being based on only 71 cancer deaths, only five of which were considered to be smoking related.

In a large case-control study of cervix cancer in Utah (64), a significant positive trend in risk was noted in relation to various indices of passive smoking exposure. There were many weaknesses in this study, including failure to adjust for religion (42% of cases and 58% of controls were Mormons), large and differential non-response rates, misclassification of smoking status, and failure to adjust adequately for sexual habits. A crude relative risk of 14.8 in relation to ETS exposure for three or more hours per day dropped to 2.96 after adjustment for the reported number of sexual partners of the woman. As number of sexual partners is only an inaccurately measured surrogate of the true sexually related cause of cervix cancer presumably a sexually transmitted infection, the adjustment will be incomplete and the excess relative risk in relation to ETS may be wholly spurious representing a residual confounding effect of sexual habits (65).

The other two studies reporting a positive association were both cited by Wells (5) and were the major contributors to his risk assessment for cancers other than the lung. The study by Sandler *et al* (66) for which Wells cites a relative risk of 2.0 based on 231 cases of cancer other than the lung, used a mixture of friends or acquaintances of patients and people randomly selected by systematic telephone sampling as controls, a very questionable procedure. Response rates also varied substantially between cases and controls. The unconvincing nature of the findings was heightened by study of the results for individual cancer sites where large effects were claimed for ETS for a number of cancers (breast, thyroid, leukaemia/lymphoma) that have little or no relationship to smoking.

The largest study is that by Hirayama (18, 52, 67). Wells (5) cites a relative risk of 1.11 (95% confidence limits 1.0-1.2) based on 2505 deaths from cancer other than the lung. This is unconvincing for a number of reasons. First, most of the comments made about this study when considering the heart disease results apply. Second, the relative risk is only at best of marginal significance (trend p = 0.05 on a one-tailed test). Third, the association with spouse smoking arises mainly because of elevated risks of brain and breast cancer, cancers that are not smoking related.

The overall evidence for cancer other than the lung is clearly remarkably unconvincing in demonstrating any effect of ETS exposure. Where any association is reported it is generally for cancer sites not affected by active smoking. Wells (5) has great (and unjustified) faith in the epidemiology, claming "these differences in mortality effects are probably real." Because it is certainly true (though as yet unquantified) that smokers have higher ETS exposure than nonsmokers it is *a priori* very difficult to see how an association with any disease could be observed only in response to ETS exposure, a

view endorsed by IARC (1). Wells argues competing risks might be the explanation, effects of ETS exposure on such cancers as brain, endocrine glands, lymphoma, and breast only occurring in people with a particular susceptibility, and that people with this susceptibility, if they smoke, die first from lung cancer or other smoking-related cancers. This seems a remarkably unattractive and implausible hypothesis, for which there is no supportive evidence. Mortality patterns for lung cancer in terms of age, dose and duration of smoking are well described by models involving no component for variation in susceptibility at all, the response arising from random variation. Of course susceptibility might in fact vary to some extent (68, 69), but hardly so much that any effect in active smokers would be ruled out. The simpler hypothesis that any relationship seen between ETS and cancer of sites other than lung is due to chance or bias seems more plausible.

EXTENDING RISK ASSESSMENT TO COVER ETS EXPOSURE FROM THE WORKPLACE

Wells (5) took account of ETS exposure outside the home in two ways in his risk assessment. First, he estimated the proportion exposed by adding the proportions of never smokers living with ever smokers (taken from the controls of the US based epidemiological studies) to the proportions of all nonsmokers who did not live with a smoker but who where still exposed at home or at work (taken from Friedman (70)). Second, he adjusted relative risk estimates upwards, except in Greece, Japan and Hong Kong, by assuming that nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers. Essentially he assumed that exposure outside the home had the same effect as exposure from the spouse.

Kawachi *et al* (6) estimated the proportion of people exposed at home and at work from surveys. From the relative risk in relation to home exposure, 1.3, they multiplied the excess relative risk, 0.3, by a factor, 4.0, based on Repace and Lowrey's estimate (34) of the relative extent of exposure to the particulate phase of ambient tobacco smoke at work (1.82 mg/day) to at home (0.45 mg/day), thus estimating relative risk of lung cancer in relation to work exposure, 2.2. They commented that "this estimate is consistent with the relative risk of 3.3 (95% confidence interval 1.0-10.5) for never smokers exposed to passive smoking at work reported by Kabat and Wynder (71) in one of the few studies that has distinguished exposure at work from exposure at home. However, we have adopted the more conservative estimate of 2.2".

It is surprising that neither Wells (5) nor Kawachi *et al* (6) seem to have actually taken into account the total epidemiological evidence on lung cancer in relation to workplace exposure. Had they done so (see Table 4) they would have found that overall it gives no indication of a positive association at all, with only four out of eleven relative risk estimates greater than 1.0 and only the single estimate (Kabat 1 - males), selectively cited by Kawachi *et al* (6) even close to being significantly positive. The upper confidence limit for seven of the eleven estimates is less than the estimate of 2.2 used in their risk assessment.

Most lung cancer cases occur at an age after people have retired. While Wells (5) adjusts the exposed fraction down with increasing age, Kawachi *et al* (6) make no such adjustment, assuming that their unjustifiably high relative risk of 2.2 in relation to workplace exposure operates at age 80 as at age 40.

The estimates by Kawachi *et al* (6) of risk due to workplace exposure from risk due to at home exposure are in any case methodologically unsound. Even assuming (and these are very big assumptions), that meta-analysis gives unbiassed estimates, that risk is linearly related to extent of exposure to smoke constituents, and that the estimates of relative exposure at work and at home are valid, the equation they used is totally incorrect. The formula only makes sense for a comparison of those exposed at work and not elsewhere with those exposed at home and not elsewhere. If at home and at work exposure are positively correlated (as is likely) double counting of deaths arises. In the extreme situation where everyone is exposed to both or to neither source, their method for estimating deaths due to at home exposure yields an answer appropriate for both exposures combined. Using their procedure, which would then multiply up deaths due to ETS by five, might lead to there being more deaths due to ETS than actually occur in all!

The validity of the factor of 4 for relative exposure at work to at home is anyway very dubious. A recent large survey in London (74) found little difference between particulate matter levels measured in the home and at work. Indeed where smoking took place, the level at work was less than at home.

TABLE 4 Reported relative risks of lung cancer in relation to ETS exposure at work.

Study	(ref)	Sex	Index of exposure	Relative risk (95% conf.limits)
Garfinkel	(42)	Female	Smoke exposure at work in last 5 years	0.88(0.66-1.18)
		Female	Smoke exposure at work in last 25 years	0.93(0.73-1.18)
Kabat 1	(71)	Female	Current exposure on regular basis to tobacco smoke at work	0.68(0.32-1.47)
		Male	Current exposure on regular basis to tobacco smoke at work	3.27(1.01-10.6)
Kabat 2	(72)	Female	Exposed to ETS at work (ever)	1.00(0.49-2.06)
		Male	Exposed to ETS at work (ever)	0.98(0.46-2.10)
Lee	(24)	Female	Passive smoke exposure at work	0.63(0.17-2.33)
		Male	Passive smoke exposure at work	1.61(0.39-6.60)
Shimizu	(73)	Female	Someone at working place smokes	1.20(0.44-1.37)
Varela	(41)	Both	150 person/years smoking in the workplace	0.91(0.80-1.04)
Wu	(20)	Female	Passive smoke exposure at work	1.3 (0.5-3.3)

OTHER ISSUES

Extension of risk assessments to workplace ETS and heart disease deaths.

While the use of epidemiological data to estimate the number of deaths from lung cancer among never smokers is dubious, extension of these estimates to other diseases and to workplace exposure is even more so. This highlights the invalidity of the estimates by Kawachi *et al* (6) where of a total of 273 deaths per year due to ETS among never smokers, only 4 are from lung cancer due to at home ETS exposure, while as many as 152 are from ischaemic heart disease due to at work ETS exposure. The fragility of the confidence limits, 112 to 442, for the overall total of 273 is obvious. In no sense can we be confident that the true answer lies in this range. The estimate is cast in an even poorer light when one realises that the factor of 4 used to calculate lung cancer relative risks at work from those at home is also used for heart disease. What is the justification for that? The basis for the factor is relative particulate matter exposure, widely thought irrelevant to heart disease aetiology. It is notable that their resultant heart disease relative risk estimates for at work exposure are, implausibly, larger than those generally reported in relation to active smoking.

Extension of risk assessments to ex-smokers.

Wells (5) and Repace and Lowrey (7) estimate numbers of deaths due to ETS among never smokers and ex-smokers combined. They assume risk estimates based on results for never smokers are applicable also to ex-smokers. Neither paper discusses the problems implicit in this approach. In the first place there is no direct epidemiological evidence on risk in relation to ETS exposure for ex-smokers with the limited exception of the study by Varela (41) which found no evidence of an effect of ETS in either never smokers or long term ex-smokers. Nor is there any evidence on levels of ETS exposure in ex-smokers as distinct from never smokers. Without direct evidence the assumption that risk increases in relation to level of ETS exposure in ex-smokers to the same extent that it does in never smokers seems remarkably simplistic. Might not effects of ex-smoking interact with those of ETS (if any)? Might not the situation depend on how long ago the smoker has given up , or why? There seems no scientific justification whatsoever for extrapolating estimates to ex-smokers.

Extrapolation from one country to another.

Kawachi *et al* (6) do not discuss the validity of calculating estimates for New Zealand when all their relevant source data comes from other countries. Their answer depends heavily on the US based factor of 4 used for relative exposure at work to at home. As noted above a UK study (68) found a factor less than 1. Which is relevant for New Zealand?

Variations in relative risk of lung cancer by age.

As discussed by Wells (5) and in the NRC report by Robins (4), if the relationship between

ETS and lung cancer risk depended on age, it would be appropriate to take this into account in the risk assessment. In fact only the study of Hirayama (18, 67) presents data by age, other investigators implicitly assuming that the relative risk is invariant of age. Using a relative risk estimate of 1.44 as applying to all age groups, Wells calculated there would be 992 deaths per year due to ETS exposure. Wells noted that Hirayama's data actually indicated "a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75" and used these data to "develop a second death calculation assuming a declining relative risk but still normalized to 1.44" arriving at a slightly lower estimate of 911 deaths per year. Wells' calculations mislead in a number of ways. First, he used as source material data on risk by age of the husband (67) when more appropriate data by age of the wife were available (18). Second, he used data for ages 60-69 and 70-79 combined as applicable at "approximately age 75", concealing the fact that the relative risk estimate at age 70-79 is actually 0.70. If one uses data in Wells' Table 6 for never smoker death rates, nonsmoker populations and fractions exposed by age, and one uses Hirayama's actual relative risks by age of the wife (18), then it can be shown (Table 5) that allowing for variation in risk by age very substantially affects estimates. Thus, for the 40-79 age group, one arrives at an estimate of 858 deaths due to ETS if one assumes age invariance, but one actually arrives at an estimate of 964 deaths saved by ETS if one uses Hirayama's data directly. The relative risk estimate for the 70-79 year age group is certainly unreliable, being based on only 6 deaths in the Hirayama study (as against 46, 91 and 57 for ages 40-49, 50-59, 60-69), so in Table 5 estimates of deaths are also shown using a combined relative risk for the age groups 60-69 and 70-79. This gives an estimate of 299 deaths due to ETS, substantially less that that assuming risk is invariant of age. While there are many problems in applying the Hirayama estimates, including the fact that Wells' Table 6 is based on age at death whereas Hirayama's data are based on age at start of the study, Wells' paper conceals the major problems which have been given detailed attention by a number of authors (75, 76). Reliable data broken down by age are clearly needed.

How many lung cancer deaths are there in total among never smokers?

In 1985 in the USA, there were a total of 83,854 deaths from lung cancer among males and 38,702 among females (77).In his Tables 6 and A1, Wells (5) gives estimates of death rates among never smokers which, if applied to the age-specific population estimates of never smokers, yield 1,907 deaths among males and 4,232 deaths among females, respectively 2.3% and 10.9% of the total deaths from lung cancer.

TABLE 5 Numbers of lung cancer deaths per year among US nonsmokers occurring in the population aged 40-79 based on Hirayama's (18) estimates of relative risk by age of wife

	Risk assumed invariant of age		Risk assumed to vary with age	
Age	Relative risk	Deaths	Relative risk*	Deaths*
40-44	1.45	32	2.76	69
45-49	1.45	40	2.76	85
50-54	1.45	58	1.72	79
55-59	1.45	89	1.72	122
60-64	1.45	119	1.12(0.97)	39(-11)
65-69	1.45	165	1.12(0.97)	54(-15)
70-74	1.45	170	0.19(0.97)	-740(-15)
75-79	1.45	185	0.19(0.97)	-672(-15)
Total		858		-964(299)

* Bracketed items assume common estimates for 60-69 and 70-79 age group.

Elsewhere (78), I have reviewed the proportion of lung cancers occurring among never smokers in a range of recent epidemiological studies of Western populations. This gave an average of 2.4% for males and 13.2% for females, equivalent to 2,012 and 5,109 deaths respectively, reasonably close to the estimates of Wells.

Other authors have suggested there are more deaths than this. Thus in the 1986 NRC report (4) Robins quoted estimates of roughly 5,200 deaths for males and 7,000 for females among U.S.

never smokers in 1985, while Repace and Lowrey (7) cite Kuller *et al* (36) for an estimate of 6000 to 8000 lung cancer cases each year in US never smoking women.

Three points arise. First, there is considerable uncertainty about the number of lung cancer deaths among never smokers.

Second, if the lower estimates, which total about 6,000-7,000 deaths in the two sexes combined, are used, then many of the epidemiologically based estimates shown in Table 2 are totally unreasonable. Even if (implausibly) everyone were assumed to be exposed to ETS with risk doubled as a result the estimated number of lung cancer deaths occurring among never smokers would only be 3,000-3,500, and yet the four highest estimates in Table 2 all exceed this.

Third, none of the estimates of total lung cancer deaths among never smokers cited above make any adjustment for misclassification of smoking status, all taking self-reported smoking habits at face value. Starting with the first estimate cited above of 6,139 deaths for the sexes combined, one can readily calculate that, if 1% of ever smokers were assumed to deny smoking on interview, this figure would fall by over a thousand to 4,972. This underlines the unreasonableness of the higher estimates in Table 2.

DISCUSSION

In the USA in 1985 there were some 120,000 deaths from lung cancer. Although estimates of the total number occurring among never smokers of up to around 12,000 have been cited, more reasonable estimates seems to be about 5,000 to 6,000. In attempting to estimate how many of these occur as a result of ETS exposure, one has to decide whether to base one's estimate on the epidemiological evidence on ETS and lung cancer or on the dosimetric evidence on exposure to relevant smoke constituents of ETS exposed nonsmokers and smokers. It is abundantly clear that the two methods of estimation give very different answers. Thus, while estimates based on retained particulate matter give tens of deaths and those based on nicotine or respirable suspended particulates give hundreds, the epidemiologically based estimates all give thousands of deaths. Which answer, if any, one accepts depends to a large extent on the faith one places on the different types of evidence. Wells (5), Kawachi *et al* (6) and Repace and Lowrey (7) accept the epidemiology essentially at face value and pay little or no attention to its poor quality and very obvious weaknesses. They either ignore the dosimetric evidence (6), do not make it clear that it gives different answers and/or dismiss it as inconsistent with the epidemiology (7), or invoke mechanisms to explain the discrepancy which are scientifically unappealing (5). It seems to this author that the epidemiological evidence is untrustworthy and that, between the two, the dosimetric evidence is preferable. Of course problems remain both in choosing the appropriate index of exposure to use and in selecting the appropriate dose response curve at low doses (with the possibility of a threshold), but it seems clear that this approach is better than one which leads to such implausibly high figures.

When one restricts attention to lung cancer, to never smokers and to ETS exposure from the spouse, one is at least operating in an area where the epidemiological evidence indicates an association. When one extends risk assessment to other diseases, to ex-smokers and to ETS exposure in the workplace one is stretching the limits of what is science. There essentially is no evidence on possible effects of ETS in ex-smokers and little reason to expect that any effects, if they exist, will be the same as in never smokers. There is some evidence on ETS exposure in the workplace, but this shows no association at all with lung cancer risk. The epidemiological evidence on ETS in relation to deaths from causes other than lung cancer is unconvincing, and no scientific authority has claimed cause and effect.

REFERENCES

1. International Agency for Research on Cancer. *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.*, 38, Tobacco Smoking, IARC, Lyon (1986).
2. National Health and Medical Research Council. *Report of the Working Party on the Effects of Passive Smoking on Health.* Australia (1986).
3. US Department of Health and Human Services. *The Health Consequences of Involuntary Smoking: a Report of the Surgeon General,* Rockville (1986).
4. National Research Council. *Environmental Tobacco Smoke. Measuring Exposure and Assessing Health Effects,* National Academy Press, Washington D.C. (1986).
5. Wells, A.J. *Environ. Int.*, **14**, 249-265 (1988).

6. Kawachi, I., Pearce, N. and Jackson, R. *N.Z. Med. J.*, **102**, 337-340 (1989).
7. Repace, J.L. and Lowrey, A.H. *Risk Anal.*, **10**, 27-37 (1990).
8. Lee, P.N. *A Detailed Review of Epidemiological Evidence relating Environmental Tobacco Smoke (ETS) to the Risk of Cancer, Heart Disease andOther Causes of Death in Adults who have Never Smoked.* In the press.
9. Inoue, R. and Hirayama, T. in *Smoking and Health 1987*, Eds. Aoki, M. et al., Elsevier, Amsterdam, 283-285 (1988).
10. Geng, G.Y., Liang, Z.H., Zhang, A.Y. and Wu, G.L. in *Smoking and Health 1987*, Eds. Aoki, M. et al., Elsevier, Amsterdam, 483-486 (1988).
11. Trichopoulos, D., Kalandidi, A. and Sparros, L. *The Lancet*, **2**, 677-678 (1983).
12. Akiba, S., Kato, H. and Blot, W.J. *Cancer Res.*, **46**, 4804-4807 (1986).
13. Brownson, R.C., Reif, J.S., Keefe, T.J., Ferguson, S.W. and Pritzl, J.A. *Am. J. Epidemiol.*, **125**, 25-34 (1987).
14. Koo, L.C., Ho, J.H-C., Saw, D. and Ho, C-Y. *Int. J. Cancer*, **39**, 162-169 (1987).
15. Lam, T.H. and Cheng, K.K. in *Smoking and Health 1987*, Eds. Aoki, M. et al., Elsevier, 279-281 (1988).
16. Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M. *Br. Med. J.*, **299**, 423-427 (1989).
17. Lam, T.H., Kung, I.T.M., Wong, C.M., Lam, W.K., Kleevens, J.W.L, Saw, D., Hsu, C., Seneviratne, S., Lam, S.Y., Lo, K.K., and Chan, W.C. *Br. J. Cancer*, **56**, 673-678 (1987).
18. Hirayama, T. in *Lung Cancer: Causes and Prevention*, Eds. Mizell, M. and Correa, P., Verlag Chemie International Inc., Deerfield Beach, 175-195 (1984).
19. Gao, Y-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F. *Int. J. Cancer*, **40**, 604-609 (1987).
20. Wu, A.H., Henderson, B.E., Pike, M.C. and Yu, M.C. *J. Nat. Cancer Inst.*, **74**, 747-751 (1985).
21. Correa, P., Pickle, L.W., Fontham, E., Lin, Y. and Haenszel, W. *The Lancet*, **2**, 595-59 (1983).
22. Humble, C.G., Samet, J.M. and Pathak, D.R. *Am. J. Public Health*, **77**, 598-602 (1987).
23. Svensson, C., Pershagen, G. and Klominek, J. *Acta Oncol.*, **28**, 623-629 (1989)
24. Lee, P.N., Chamberlain, J. and Alderson, M.R. *Br. J. Cancer*, **54**, 97-105 (1986)
25. Buffler, P.A., Pickle, L.W., Mason, T.J. and Contant, C. in *Lung Cancer Causes and Prevention*, Eds. Mizell, M. and Correa, P. Verlag Chemie International Inc., Amsterdam, 83-89 (1984).
26. Chan, W.C. and Fung, S.C. in *Cancer Epidemiology*, Gustav Fischer Verlag, Vol 6, 199-202 (1982).
27. Lee, P.N. *Human Toxicol.*, **6**, 517-524 (1987).
28. Wald, N.J., Nanchahal, K. and Cuckle, H. *Br. J. Cancer*, **61**, 337-344 (1990),
29. Arundel, A., Irwin, T. and Sterling, T. *J. Environ. Sci. Health*, Part C, **4**, 93-118 (1986),
30. McAughey, J.J., Pritchard, J.N. and Black, A. in *Present and Future of Indoor Air Quality*, Eds. Bieva, C.J. et al., Excerpta Medica International Congress Series 860, Brussels, 161-168 (1989).
31. Adlkofer, F.X., Scherer, G., von Meyerinck, L., von Maltzan, Ch. and Jarczyk, L. in *Present and Future of Indoor Air Quality*, Eds. Bieva, C.J. *et al.* Excerpta Medica International Congress Series 860, Brussels, 189-196 (1989).
32. Fong, P. *J. Biol. Phys.*, **10**, 65-73 (1982).
33. Wald, N.J., Nanchahal, K., Thompson, S.G. and Cuckle, H.S. *Br. Med. J.*, **293**, 1217-1222 (1986).
34. Repace, J.L. and Lowrey, A.H. *Environ. Int.*, **11**, 3-22 (1985).
35. Wigle, D., Collishaw, N., Kirkbride, J. and Mao, Y. *Can. Med. Assoc. J.*, **136**, 945-951 (1987).
36. Kuller, L.H., Garfinkel, L., Correa, P., Preston-Martin, S., Haley, N.J., Sandler, D.P. and Hoffmann, D. *Environ. Health Perspect.*, **70**, 57-69 (1986).
37. Russell, M.A.H., Jarvis, M.J. and West, R.J. *Br. J. Addict.*, **81**, 275-281 (1986).
38. Lee, P.N. in *Assessment of Inhalation Hazards*, Eds. Mohr, U. et al., ILSI Monographs, Springer-Verlag, Berlin, 49-59 (1989).
39. Faccini, J. Exp. *Pathol.*, **37**, 177-180 (1989).
40. Begg, C.B. and Berlin, J.A. *J. R. Stat. Soc. Ser. A*, **151**, 419-463 (1988).

41. Varela, L.R. "Assessment of the Association between Passive Smoking and Lung Cancer.", Yale University Doctor of Philosophy Dissertation (1987).
42. Garfinkel, L., Auerbach, O. and Joubert, L. *J. Nat. Cancer Inst.*, **75**, 463-469 (1985).
43. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S. *Gan No Rinsho*, **36**, 329-333 (1990).
44. Koo, L.C., Ho, J.H-C. and Rylander, R. *Soc. Sci. Med.*, **26**, 751-760 (1988).
45. Lee, P.N. *Misclassification of Smoking Habits and Passive Smoking. A Review of the Evidence.* Springer-Verlag, Heidelberg, (1988).
46. Saito, R. in *Smoking and Health 1987*, Eds. Aoki, M. et al., Elsevier, 517-519 (1988).
47. Gillis, C.R., Hole, D.J., Hawthorne, V. and Boyle, P. *Eur. J. Respir. Dis.(Suppl.133)*, **65**, 121-126 (1984).
48. Garland, C., Barrett-Connor, E.,Suarez, L., Criqui, M.H. and Wingard, D.L. *Am. J. Epidemiol.*, **121**, 645-650 (1985).
49. Helsing, K.J., Sandler, D.P., Comstock, G.W. and Chee, E. *Am. J. Epidemiol.*, **127**, 915-922 (1988).
50. Svendsen, K.H., Kuller, L.H., Martin, M.J. and Ockene, J.K. *Am. J. Epidemiol.*, **126**, 783-795 (1987).
51. Martin, M.J., Hunt, S.C. and Williams, R.R. Annual Meeting of American Public Health Association (1986).
52. Hirayama, T. *Br. Med. J.*, **282**, 183-185 (1981).
53. Layard, M.W. and Viren, J.R. in *Present and Future of Indoor Air Quality*, Eds. Bieva, C.J. *et al.*, Excerpta Medica International Congress Series 860, Brussels, 177-180 (1989).
54. Lee, P.N. *Br. Med. J.*, **283**, 1465-1466 (1981).
55. Lee, P.N. (1989) *N.Z. Med. J.*, **102**, 539 (1989).
56. Hirayama, T. *N.Z. Med. J.*, **103**, 54 (1990).
57. Garfinkel, L. *J. Nat. Cancer Inst.*, **66**, 1061-1066 (1981).
58. Burch, J.D., Rohan, T.E., Howe, G.R., Risch, H.A., Hill, G.B., Steele, R. and Miller, A.B. *Int. J. Cancer*, **44**, 622-628 (1989).
59. Kabat, G.C., Dieck, G.S. and Wynder, E.L. *Cancer*, **57**, 362-367 (1986).
60. Hellberg, D., Valentin, J. and Nilsson, S. *The Lancet*, **2**, 1497 (1983).
61. Miller, G.H. *West J. Med.*, **140**, 632-635 (1984).
62. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L. *Am. J. Public Health*, **79**, 163-167, (1989).
63. Reynolds, P., Kaplan, G.A. and Cohen, R.D. Society for Epidemiological Research, Amherst, Massachusetts (1987).
64. Slattery, M.L., Robison, L.M., Schuman, K.L., French, T.K., Abbott, T.M., Overall, J.C. and Gardner, J.W. *JAMA*, **261**, 1593-1598 (1989).
65. Layde, P.M. *JAMA*, **261**, 1631-1633 (1989).
66. Sandler, D.P., Everson, R.B. and Wilcox, A.J. *Am. J. Epidemiol.*, **121**, 37-48 (1985).
67. Hirayama, T. *Prev. Med.*, **13**, 680-690 (1984).
68. Caporaso, N.E., Tucker, M.A., Hoover, R.N., Hayes, R.B., Pickle, L.W., Issaq, H.J., Muschik, G.M., Green-Gallo, L., Buivys, D., Aisner, S., Resau, J.H., Trump, B.F., Tollerud, D., Weston, A. and Harris, C.C. *J. Nat. Cancer Inst.*, **82**, 1264-1272 (1990).
69. Sellers, T.A., Bailey-Wilson, J.E., Elston, R.C., Wilson, A.F., Elston, G.Z., Ooi, W.L. and Rothschild, H. *J. Nat. Cancer Inst.*, **82**, 1272-1279 (1990).
70. Friedman, G.D., Pettiti, D.B. and Bawol, R.D. *Am. J. Public Health*, **73**, 401-405 (1983)
71. Kabat, G.C. and Wynder, E.L. *Cancer*, **53**, 1214-1221 (1984).
72. Kabat, G.C. 1990 Winter Toxicology Forum, Washington D.C. (1990).
73. Shimizu, H., Morishita, M., Mizumo, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishimo, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisanichi, S. and Tominaga, S. *Tohoku J. Exp. Med.*, **154**, 389-397 (1988).
74. Kirk, P.W.W., Hunter, M., Baek, S.O., Lester, J.N. and Perry, R. in *Indoor and Ambient Air Quality*, Eds. Perry, R. and Kirk, P.W. Selper, London, 99-112 (1988).
75. Ahlborn, W. and Uberla, K. in *Indoor and Ambient Air Quality*, Eds. Perry, R.and Kirk, P.W. Selper, London, 169-178 (1988).

76. Kilpatrick, S.J. and Viren, J. in *Indoor and Ambient Air Quality*, Eds. Perry, R. and Kirk, P.W., Selper, London, 195-202 (1988).
77. World Health Organisation. *1988 World Health Statistics Annual*, Geneva (1988).
78. Lee, P.N. Unpublished results (1990).